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Description of a Case of Thalassemia Major and the Effects of Splenectomy

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Edward Atkinson Nichols
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Description of a Case of Thalassemia Major and the Effects of Splenectomy

In 1925, *Thomas B. Cooley* described cases (13) of a microcytic anemia with splenomegaly and peculiar bone changes in children of Italian immigrants. He proposed the name «Erythroblastic Anemia". In the same year, *Rietti, Greppi and Micheli* (40) reported an hemolytic anemia among the inhabitants of the province of Ferrara near the delta of the Po river. In 1936, *Whipple and Bradford* (49) *introduced* the picturesque although inaccurate greek word for "Sea" in the form of "Thalassemia" in reference to the prevalence of the disease among the inhabitants and descendants of the mediterranean basin where it has been widely described (11, 12, 42). It has since been described in a host of diverse geographical and racial areas as far removed as in America among Indians and Negroes, in Switzerland, in India and in the Far East (4, 36, 10, 34, 6b, 20, see Fig. 1). 1935 *Frontali* (22a) pointed out the analogous relation of the two syndromes and noted that they differed essentially only in degrees of manifestation. *Gatto* (23) proposed the name thalassemia minima in which the symptoms presented in a milder form. *Silvestroni and Bianco* (43a) offered the more descriptive name microcythemia. *Frontali* (22b) suggested the name thalassemia major for Cooley's anemia and thalassemia minor for the hemolytic icterus of Rieti. Since then, a number of other clinical variants have been described which fit into the thalassemia syndrome. Until 1942, less than 100 cases of Cooley's anemia had been reported (50). *Neel and Valentine* (37a, b) found the incidence of the gene for thalassemia major in 0.042% and the gene for thalassemia minor in 4% of the Italian

immigrant population in Rochester, New York. The incidence of thalassemia in communities near Ferrara was recorded as high as 20%. The distribution of the genes for thalassemia throughout the world has been attributed to historical migrations of peoples, wars and the flow of trade throughout the centuries.

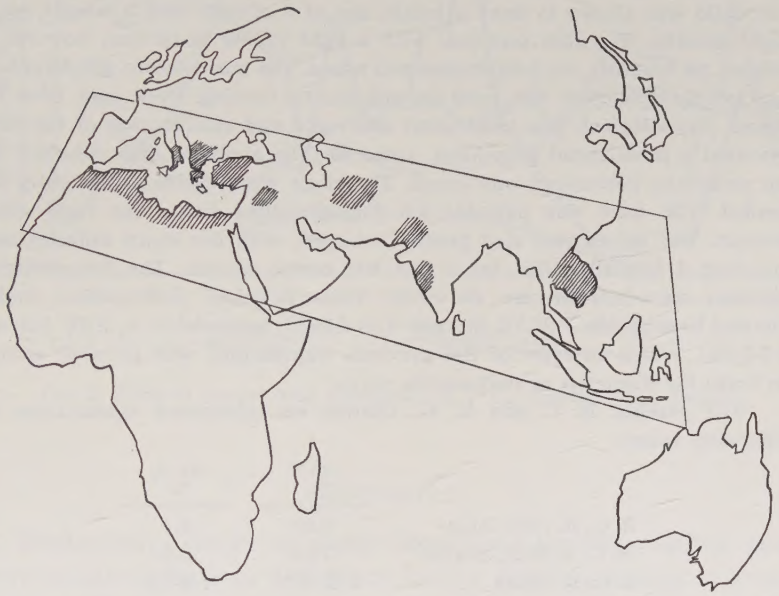

Fig. 1. Geographic distribution of the Thalassemia genes in Europe, Africa, and Asia.

The current interest in thalassemia and the rarity of this disease in Switzerland has given us cause to present a short review of the literature regarding the advances in diagnosis, pathogenesis and treatment which we shall illustrate with one of our own cases.

Case Report

V. C. is a sixteen month old male infant, transferred to our hospital from another clinic. There, hematological examination revealed a hemoglobin of 29%, 1,500,00 red blood cells, pronounced anisocytosis, poikilocytosis and polychromasia. The assumed diagnosis was thalassemia major. The child was given blood transfusion and corticosteroids. The hemoglobin level responded adequately and the spleen became smaller. The family history revealed that both parents of the boy V. C. are Italians from the vicinity of Venice. The father has had malaria. One of the father's two brothers, has an acquired

blindness and the other tuberculosis of the lung. While the mother herself has always been healthy, one sister died of meningitis, one brother reportedly has a child with anemia. The infant V. C. was born at term in Contarino (near Venice). At six months an enlarged abdomen was noticed for the first time. During the first year, the child developed normally. Since then he has shown a noticeable retardation of growth and increasing pallor, for which he was finally admitted in a clinic elsewhere. On transfer to our hospital the child was shown to have a height age of 9 months and a weight age of eight months. The skin was pale with a light yellow undertone, however no edema, no cyanosis, no dehydration was noted. The musculature was hypotonic and poorly developed. The head showed frontal bossing. Eyes, ears, nose and throat physiological. The respiration was rapid and examination of the heart revealed a pronounced arhythmia, pulse 80. The abdomen was enlarged, but no ascites on percussion was found. The venes were visible and slightly distended. The liver was palpable 4-5 fingerbreadths below the right costal margin. The spleen was also grossly enlarged, with the sharp anterior edge reaching 4 fingerbreadths below the left costal margin. The hematological findings on admission are shown in Table I. Alkali denaturation studies showed hemoglobin F 25.5% (normal 0.25-0.75%), hemoglobin A_2 2.3% (normal 1.0-3.0%), which in spite of the previous transfusions was elevated enough to make the diagnosis of thalassemia major.

The parents, R. C. and M. C., showed on subsequent examination the following values:

	Hb F %	Hb A_2 %
R. C., b. 1927, father	0.42	5.1
M. C., b. 1933, mother	1.14	5.6
normal values	0.25-0.75	1.0-3.0

revealing the presence of thalassemia minor in both otherwise healthy parents.

The increased breakdown of red cells is demonstrated in the shortened survival of Cr_{51} tagged erythrocytes which showed a half life of 18 days (normal 26-34 days), and in the high urobilinogen excretion of 79.3 mg per day in the feces, i.e. over 200 mg per 100 g circulating hemoglobin.

Roentgenograms of the hand showed rarification of the metacarpals and phalanges. A widening of the os frontale was also present.

In the course of four weeks, the hemoglobin sank (see Chart) from a value of 65% on admission to 28%, so that a transfusion of 90 cc of whole blood was administered. A erythropoetic stimulation was noted in response to small doses of corticosteroids. For three months the hemoglobin level remained relatively stable at 35-40%. During this time the splenomegaly increased until it was elected to perform a splenectomy. This was done on 23. 8. 1961, with antibiotic support and a transfusion of 400 cc whole blood. The post operative hemoglobin was 70% and remained around 60% for six weeks. The appetite and general condition improved. In one month after the operation, the child's weight increased from 8.6 to 9.78 kilograms. On October 30, the child was given a blood transfusion of 200 cc whole blood and discharged on the 8th of November.

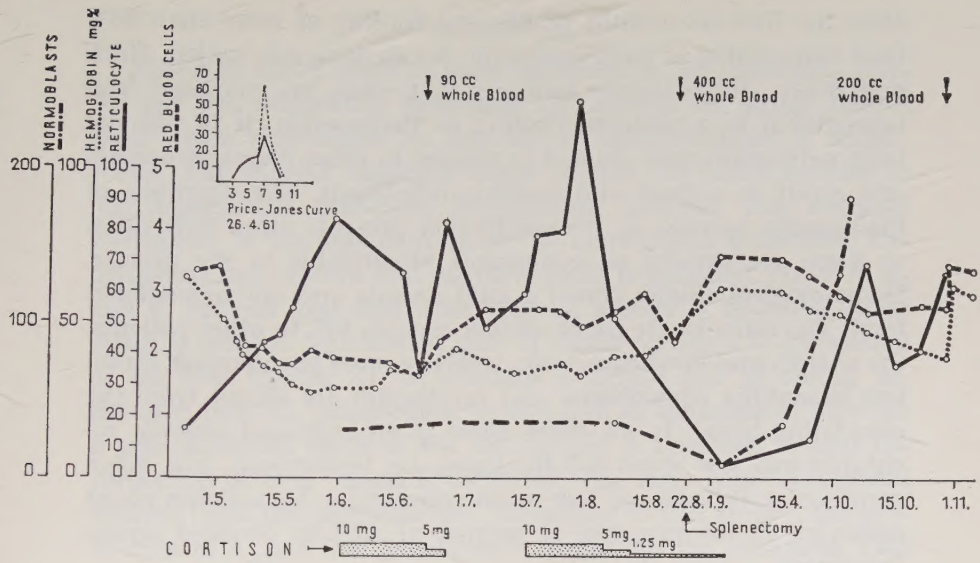

Fig. 2. Clinical course and treatment of V. C., Kinderspital, Basle

Diagnosis 1

Thalassemia major is easily diagnosed by the clinical and morphological features and from family studies. *Astaldi* and co-workers (2) separated three grades of severity in thalassemia. The severe form with the child usually dying in the first year. A milder form is diagnosed in the second half of the first year, with survival of the child until the fifth or sixth year. A still milder form becomes manifest usually after the second year and is compatible with survival into adult life. In the two latter forms, bone changes due to secondary hyperplasia are found. Laboratory procedures have been used effectively since *Vecchio* (47) proved that the hemoglobin in children suffering from *Cooley*'s anemia showed a 60-90% increase in its resistance to alkali. Other authors claim that the increased resistance together with an increase in the number of circulating basophilic erythroblasts constitute diagnostic proof of abortive forms of Cooley's anemia with atypical hematological findings (41, 49, 50). The significance of the increase in fetal hemoglobin in the diagnosis of thalassemia major was first reported by *Caminopetros* (8) in 1938 and confirmed by *Averse* (3) in electrophoretic studies. It was pointed out that

after the first six months of life, the finding of more than 35% fetal hemoglobin is pathognomonic for thalassemia major. *Marti and Betke* (36) maintain however that while an increased fetal hemoglobin is a common finding in thalassemia, it is still not fully pathognomonic, since it is present in other forms of anemia and rarely in normal and healthy individuals. The diagnosis of thalassemia minima or microcythemia presents more difficulties as there are usually no complaints attributable to the disease, Hematological studies reveal a mild anemia and low hemoglobin level. The reticulocyte count seldom exceeds 5%. In other patients, the anemia and low hemoglobin level are more pronounced. Punctate basophilia normoblasts and myelocytes are absent from the circulating blood. In all cases, there is an increased osmotic resistance and low mean cell thickness, i.e. leptocytosis, low mean corpuscular volume and low mean corpuscular hemoglobin count occurring in the presence of normal or slightly elevated serum iron levels.

Diagnosis 2

Characteristic of the Rietti form of thalassemia minor are the mild chronic jaundice and splenomegaly. Relatively inconstant findings are leg ulcers and gallstones. Roentgenograms may show osteoporosis. In 1958, *Gerald and Diamond* (24) stressed the diagnostic significance of increase amounts of the electrophoretically slow moving hemoglobin A_2 for the detection of carriers of the thalassemia genes. This type of hemoglobin is normally present in small amounts, ($2.54 \pm 0.35\%$), but in heterozygous thalassemia, increased values (more than 3,0%), are found in association with microcytosis. The separation of mediterranean anemia from the hemoglobinopathies such as hemoglobin S and hemoglobin C disease and mixed syndromes such as the combination hemoglobin S/thalassemia can be adequately accomplished by demonstrating the extreme slowness of mobility of these abnormal hemoglobins in electrophoretic studies. Elliptocytosis is diagnosed by the presence of elliptic erythrocytes in the blood smears of an otherwise healthy individual. In Spherocytosis, there are characteristic hemolytic crises. The color index is 1, and the osmotic resistance is decreased. The widening of the diploe in the skull, the broadening of the nose and the prominence of the cheekbones seen in thalassemia major are rare in this disease.

Pathogenesis 1

Although many theories have appeared in the literature, (21), not one has adequately described and proven the prime pathogenic lesion responsible for the clinical manifestations of thalassemia. The current concepts center around the abnormalities in the hemoglobin molecule, Biochemical analysis has revealed alterations in the side chaines of the hemoglobin molecules. Experiments have shown that the three main hemoglobin types, A, A_2 and F, contain four side chains. In all groups, a so-called alpha chain is present. The second pair of chains in Hb A is designated as the beta chains. Hb A_2 contains a second pair of chains designated that the pathological mechanism of thalassemia involves a gene mutation block of the hemoglobin A synthesis so that the formation of beta chains is inhibited. The term beta-thalassemia evolves from this phenomenon. According to this theory, the production of A_2 and fetal hemoglobin would then be enhanced. This theory is supported by *Braunitzer* and co-workers (7) and *Lehmann* (32). In studies of double heterozygote pedigrees however, *Huisman* (27) showed that there can be a suppression of hemoglobinA synthesis, in the absence of an elevation of hemoglobin A_2. *Ingram and Stretton* (29a, b) proposed that there is a "common pathway" in the development of the hemoglobin side chains. Initially, the production of gamma chains (Hb F) predominates, with a subsequent shift to delta chains (Hb A_2) and finally the adult type beta chains (Hb A). Furthermore, he proposed that in thalassemia, this stepwise synthesis is blocked by gene mutations responsible for the production of these chains resulting in the increaed formation of hemoglobin of the preceding stage. Zuelzer augmented these findings (52 b), describing thalassemia patients with results pointing to the possible presence of two genes producing reciprocal amounts of Hb A_2 and Hb F in two pedigrees. Thus an abnormal beta chain can exist without coexisting changes in Hb A_2 and Hb F synthesis and the abnormal delta chain gene will affect only Hb A_2 and not the other genes. Interference in the production of all three hemoglobin types occur in the so-called alpha thalassemia affecting only alpha chain synthesis.

Pathogenesis 2

The clinical manifestations of thalassemia are attributable to a defect in red cell formation. These cells are small, flaccid with

little cytoplasmic substance and extremely small mean cell thickness, for which *Dameshek* (15) gave the name "Leptocytosis» leading to the formation of target cells. The increased osmotic resistance is explained by the increased capacity of the cells to absorb fluid without bursting. The increased mechanical fragility and tendency to form schistocytes are held responsible at least in part for the increased destruction of erythrocytes in thalassemia major. *Frontali and Stegagno* (22 a) demonstrated the shortened life span of red cells in thalassemia patients. The spleen is assumed to play a major role in their destruction, but other authors (48) do not share this viewpoint. The increased hemolysis leads to a secondary hyperplasia of the bone marrow, which is nevertheless inadequate in thalassemia major. The conversion of glycine to gamma aminolevulinic acid and the binding of protoporphyrin, iron, heme and globin to form hemoglobin is defective which results in an impaired production of red blood cells (46) even in the presence of normal serum iron levels (35). *Bannerman, Grinstein and Moore* (5) have noted the same slowing in the rate of protoporphyrin synthesis and a partial block in the combination of protoporphyrin and iron in vivo. Crosby and Akeroyd demonstrated a decreased production of red blood cells in three cases of thalassemia major. In morphological studies of thalassemia major using the electron microscope, *Hoffman* et al. (26) showed the surface of the thalassemia major red blood cells to be of an abnormal coarseness. They failed to note this phenomenon in the surface texture of thalassemia minor cells. *Astaldi* (2, 2a, b) and others demonstrated an abnormal glucomucoprotein substance in the cytoplasm of erythroblasts in thalassemia major.

Treatment and Prognosis

In thalassemia patients, there are no beneficial effects of various forms of anti-anemia therapy, including folic acid, cobalt, copper, vitamin B_{12}, or other organ extracts. Transfusions have a place in the therapy of thalassemia major, to counteract the hemolysis (52 c) and the inadequate compensatory erythropoesis (14). In the long run, however, this too proves inadequate, because of the increasing transfusion requirements necessary to maintain a suitable hemoglobin level compatible with normal activity. In the course of time, an extracorpuscular hemolytic mechanism can

develop (33) with the concomitant danger of hemosiderosis. Eventually, splenectomy must be considered (19, 39). A further indication for splenectomy in the form of the gross enlargement of the spleen was pointed out by *Smith and others* (39, 45 b, 51). In patients with marked hemolysis, the effects following splenectomy have been best. The survival times of donor cells increase from a half-life of 10-19 days (normal 26 days), to a post splenectomy value of 25-34 days) (48). Greater amounts of fetal hemoglobin and adult hemoglobin are found in the post splenectomy period. This is understood as a suppression of the pre-existing hypersplenism. The effect of the operation is reflected favourably by the reduced transfusion requirements. The mean interval between transfusions was six weeks (48), as compared to 6-8 weeks found in our patient. Several patients are able to go with transfusion for 1-5 years. The common occurrence of infection in the two year period following operation was pointed out by *Huntley* (28) and later *Smith* (45 b). For this reason, Antibiotics can be given prophylactically during this time.

The prognosis of severe cases of Cooley's anemia is very poor. Death usually is due to an intercurrent infection. The milder forms classified under the thalassemia syndrome do reach adolescence, and some have reached adult life.

Summary

We have presented a case of Thalassemia major in a sixteen month old Italian infant that was admitted to our hospital. Hematological findings showed a red blood cell count of 3,350,000, an hemoglobin level of 65%, microcytosis, anisocytosis, poikilocytosis, target cells, increased reticulocyte count and increased osmotic resistence. Laboratory procedures revealed an increased Hb F of 25.5%, and an Hb A_2 of 2.3%. The life span of Cr_{51} tagged erythrocytes was shortened ($^1/_2$ life 18 days). Clinically, the patient showed a pallor, a retardation of growth and a pronounced hepatosplenomegaly. A splenectomy was performed to alleviate the mechanical effects of splenomegaly and to increase the interval between transfusions. The case was discussed in light of the new advances in diagnosis, pathogenesis and treatment of the disease.

Zusammenfassung

Bei einem 16 Monate alten Italiener wurde eine Thalassemia major festgestellt. Die haematologischen Befunde, wie Microcytose, Anisocytose, Poikilocytose, Target-Zellen, vermehrte Reticulocytose und vermehrte osmotische Resistenz, werden beschrieben. Ferner ein erhöhter Hb F-Gehalt von 25,5% und

Hb A_2 von 2,3 %. Die mit Cr_{51} markierten Erythrocyten zeigten eine verkürzte Lebensdauer von 18 Tagen. Die klassischen klinischen Befunde waren alle vorhanden. Es wurde eine Splenectomie durchgeführt, um die mechanische Behinderung durch die Riesenmilz zu eliminieren und den Intervall zwischen den einzelnen Transfusionen zu verlängern. Der Fall wurde im Lichte der neuen Fortschritte auf dem Gebiet der Diagnose, Pathogenese und Behandlung der Krankheit diskutiert.

Résumé

Les auteurs présentent un cas de thalassémie majeure chez un enfant âgé de 16 mois, d'origine italienne. Les globules rouges s'élevaient à 3.350.000 et l'hémoglobine à 65 % ; il y avait de plus une microcytose, une anisocytose, une poïkilocytose, des «.target cells », un nombre augmenté de réticulocytes et une résistance osmotique. Les autres examens de laboratoire révélèrent un taux élevé d'hémoglobine F (25,5 %) et d'hémoglobine A_2 (2,3 %). La durée de vie des érythrocytes, marqués au Cr_{51}, était raccourcie.

Au point de vue clinique, le patient présentait une pâleur, un retard de croissance et une hépatosplénomégalie prononcée.

On a procédé à une splénectomie pour supprimer les effets mécaniques de la splénomégalie et pour accroître l'intervalle entre les transfusions.

Le cas est discuté à la lumière des récents progrès en diagnostic, pathogénèse et traitement de cette affection.

Resumen

Los autores presentan un caso de talasemia mayor en un níño italiano de 16 meses. Desde el punto de vista hematológico se constató un número de hematíes de 3.350.000, un nivel de hemoglobina de 65%, microcitosis, anisocitosis, poiquilocitosis, dianocitos, aumento de reticulocitos e incremento de la resistencia osmótica. Los exámenes de laboratorio relevaron un aumento de Hb F en un 25 % y de HB A_2 en un 2,3 %. El tiempo de vida de los eritrocitos marcados con Cr_{51} estaba acortado (½ vida, 18 dias). Clínicamente el paciente mostraba palidez, retardo del crecimiento y pronunciada hepato-esplenomegalia. Se realizó la esplenectomía para suprimir los efectos mécanicos de la esplenomegalia y aumentar el intérvalo entre las transfusiones. Se comenta la observación teniendo en cuanta los nuevos avances en el diagnóstico, patogénesis tratamiento de la enfermedad.

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Author's address: Dr. E. A. Nichols, Universitäts-Kinderklinik, *Basel* (Schweiz).